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Folpet; CASRN 133-07-3

Human health assessment information on a chemical substance is included in the IRIS database only after a comprehensive review of toxicity data, as outlined in the [IRIS assessment development process](#). Sections I (Health Hazard Assessments for Noncarcinogenic Effects) and II (Carcinogenicity Assessment for Lifetime Exposure) present the conclusions that were reached during the assessment development process. Supporting information and explanations of the methods used to derive the values given in IRIS are provided in the [guidance documents located on the IRIS website](#).

STATUS OF DATA FOR Folpet

File First On-Line 09/30/1987

Category (section)	Assessment Available?	Last Revised
Oral RfD (I.A.)	yes	09/30/1987
Inhalation RfC (I.B.)	not evaluated	
Carcinogenicity Assessment (II.)	yes	08/22/1988

I. Chronic Health Hazard Assessments for Noncarcinogenic Effects

I.A. Reference Dose for Chronic Oral Exposure (RfD)

Substance Name — Folpet
CASRN — 133-07-3
Last Revised — 09/30/1987

The oral Reference Dose (RfD) is based on the assumption that thresholds exist for certain toxic effects such as cellular necrosis. It is expressed in units of mg/kg-day. In general, the RfD is an estimate (with uncertainty spanning perhaps an order of magnitude) of a daily exposure to the human population (including sensitive subgroups) that is likely to be without an appreciable risk of deleterious effects during a lifetime. Please refer to the Background Document for an elaboration of these concepts. RfDs can also be derived for the noncarcinogenic health effects of

substances that are also carcinogens. Therefore, it is essential to refer to other sources of information concerning the carcinogenicity of this substance. If the U.S. EPA has evaluated this substance for potential human carcinogenicity, a summary of that evaluation will be contained in Section II of this file.

I.A.1. Oral RfD Summary

Critical Effect	Experimental Doses*	UF	MF	RfD
Decreased body weight gain, altered serum chemistry parameters	NOEL: 10 mg/kg/day LEL: 60 mg/kg/day	100	1	1E-1 mg/kg/day
Chronic Oral Toxicity Study in Dogs				
Chevron Chemical, 1986				

*Conversion Factors: none

I.A.2. Principal and Supporting Studies (Oral RfD)

Chevron Chemical Company. 1986. MRID No. 00161345. Available from EPA. Write to FOI, EPA, Washington, DC 20460.

Groups of six male and six female dogs were given doses of 0, 10, 60, or 120 mg/kg/day of folpet in gelatin capsules for 1-year. A NOEL for systemic effects of 10 mg/kg/day was established based on decreases in food consumption and body weight gain, and decreases in serum cholesterol, total protein, and serum albumin and globulin levels in dogs given doses of 60 or 120 mg/kg/day.

I.A.3. Uncertainty and Modifying Factors (Oral RfD)

UF — An uncertainty factor of 100 was used to account for intra- and interspecies differences in sensitivity.

MF — None

I.A.4. Additional Comments (Oral RfD)

Data Considered for Establishing the RfD:

- 1) Chronic Oral Toxicity - dog: Principal study - see previous description; core grade minimum
- 2) 2-Generation Reproduction - rat: Reproductive NOEL=690 ppm (34.5 mg/kg/day); Reproductive LEL=3200 ppm analytical (160 mg/kg/day) (decreased male fertility); core grade guideline (Chevron Chemical Co., 1985a)
- 3) 2-Year Feeding - rat: NOEL=200 ppm (10 mg/kg/day); LEL=800 ppm (40 mg/kg/day) (Ulceration/erosion and hyperkeratosis of the nonglandular stomach); core grade supplementary (diet analyses requested) (Chevron Chemical Co., 1985b)
- 4) Teratology - rat: Developmental NOEL=60 mg/kg/day; Developmental LEL=360 mg/kg/day (incomplete ossification); Maternal NOEL=10 mg/kg/day; Maternal LEL=60 mg/kg/day (decreased weight gain); core grade guideline (Chevron Chemical Co., 1983)
- 5) Teratology - rabbit (New Zealand White): Developmental NOEL=10 mg/kg/day; Developmental LEL=20 mg/kg/day (hydrocephalus, skull bone defects); Maternal NOEL=10 mg/kg/day; Maternal LEL=20 mg/kg/day (decreased food consumption and weight gain); core grade minimum (Chevron Chemical Co., 1984)
- 6) Teratology - rabbit (HY/CR): Developmental NOEL=10 mg/kg/day; Developmental LEL=40 mg/kg/day (delayed ossification, no evidence of hydrocephalus or other skull defects noted); Maternal NOEL=40 mg/kg/day; Maternal LEL=160 mg/kg/day (decreased weight gain, clinical signs); core grade supplementary (clarification, historical data requested) (Chevron Chemical Co., 1985c)

Data Gap(s): Chronic feeding - rat (additional data requested); Additional data on potential reproductive effects in the mouse

I.A.5. Confidence in the Oral RfD

Study — High

Database — High

RfD — High

The principal study is considered of high quality, and the database is complete and contains studies of good quality. Therefore, the chosen study, the database and the RfD are all given high confidence ratings.

I.A.6. EPA Documentation and Review of the Oral RfD

Pesticide Registration Standard, 1986

Pesticide Registration Files

Agency Work Group Review — 02/18/1987, 05/20/1987

Verification Date — 05/20/1987

Screening-Level Literature Review Findings — A screening-level review conducted by an EPA contractor of the more recent toxicology literature pertinent to the RfD for Folpet conducted in November 2001 did not identify any critical new studies. IRIS users who know of important new studies may provide that information to the IRIS Hotline at hotline.iris@epa.gov or (202)566-1676.

I.A.7. EPA Contacts (Oral RfD)

Please contact the IRIS Hotline for all questions concerning this assessment or IRIS, in general, at (202)566-1676 (phone), (202)566-1749 (FAX) or hotline.iris@epa.gov (internet address).

I.B. Reference Concentration for Chronic Inhalation Exposure (RfC)

Substance Name — Folpet

CASRN — 133-07-3

Not available at this time.

II. Carcinogenicity Assessment for Lifetime Exposure

Substance Name — Folpet

CASRN — 133-07-3

Last Revised — 08/22/1988

Section II provides information on three aspects of the carcinogenic assessment for the substance in question; the weight-of-evidence judgment of the likelihood that the substance is a human carcinogen, and quantitative estimates of risk from oral exposure and from inhalation exposure. The quantitative risk estimates are presented in three ways. The slope factor is the result of application of a low-dose extrapolation procedure and is presented as the risk per (mg/kg)/day. The unit risk is the quantitative estimate in terms of either risk per ug/L drinking water or risk per ug/cu.m air breathed. The third form in which risk is presented is a drinking water or air concentration providing cancer risks of 1 in 10,000, 1 in 100,000 or 1 in 1,000,000. The rationale and methods used to develop the carcinogenicity information in IRIS are described in The Risk Assessment Guidelines of 1986 (EPA/600/8-87/045) and in the IRIS Background Document. IRIS summaries developed since the publication of EPA's more recent Proposed Guidelines for Carcinogen Risk Assessment also utilize those Guidelines where indicated (Federal Register 61(79):17960-18011, April 23, 1996). Users are referred to Section I of this IRIS file for information on long-term toxic effects other than carcinogenicity.

II.A. Evidence for Human Carcinogenicity

II.A.1. Weight-of-Evidence Characterization

Classification — B2; probable human carcinogen

Basis — Folpet has induced carcinoma and adenoma of the duodenum (an unusual site) in both sexes of both CD-1 and B6C3F1 mice. Folpet is also mutagenic in several in vitro assays and is a structural analogue of captan, which has been shown to induce carcinoma in the duodenum of two mouse strains.

II.A.2. Human Carcinogenicity Data

None

II.A.3. Animal Carcinogenicity Data

Sufficient. Several Carcinogenicity studies of folpet in several strains of mice and rats have been conducted. Folpet was fed at 0, 1000, 5000 or 12,000 ppm to CD-1 mice (80/sex/dose group and 104/sex in the controls) for 112-113 weeks (Chevron, 1982). When compared with concurrent controls, adenocarcinomas of the duodenum were increased in the females fed the mid-dose ($p < 0.05$) and high-dose ($p < 0.01$) and in the males fed the mid- and high-dose ($p < 0.01$). The incidence of adenomas was increased ($p < 0.01$) in both sexes at the high dose. Dose-related increases in carcinoma incidences in all male treatment groups, and in females fed the mid- and high-dose, were accompanied by a dose-related increase in mucosal hyperplasia and proliferation

of glandular tissue of the duodenum. The incidence of papillomas of the nonglandular stomach tissue were also significantly increased in females. In addition, tumors of the jejunum, ileum, cecum and colon were also observed in treated mice of each sex. The overall incidence of digestive tract tumors for both sexes at the high dose was 51%, compared with <1% for concurrent and historical controls. At the mid-dose the MTD appears to have been achieved based on a 10% decrease in body weight. At the high dose, the MTD may have been exceeded.

Charles River B6C3F1 mice (52 sex/group) were fed folpet for 21 weeks at 0, 1000, 5000 or 10,000 ppm (Makhteshim, 1985). Due to toxicity, the mid- and high-doses were lowered at week 22 to 3500 and 7000 ppm and remained at these levels for the balance of the study (104 weeks), producing a TWA for the mid and high doses of approximately 3800 and 7600 ppm, respectively. A dose-related increase in the incidence of carcinoma of the duodenum was observed in all dosage groups. This was accompanied by a slight increase in the incidence of adenomas of the duodenum and a dose-related increase in the incidence of mucosal hyperplasia and glandular tissue proliferation. A statistically significant ($p < 0.05$) increase in the incidence of papillomas of the nonglandular stomach was seen in the females. Females at the high dose had a statistically significant increase in the incidence of malignant lymphoma; however, in the males, a statistically significant decrease was observed for this finding. The MTD appears to have been exceeded at the high dose as evidenced by a 25% decrease in body weight, but neoplasia were seen at all dosage levels.

As part of a large study of pesticides (Innes et al., 1969), 18 B6C3F1 mice of both sexes, and 18 B6AKF1 mice of both sexes were administered 215 mg/kg/day of folpet by intubation from days 7-28 of age followed by 603 ppm folpet in the diet through 18 months of age. The incidence of tumors in the treated mice was no greater than control group of 80 mice. It is possible that folpet may have been inactivated by the gelatin vehicle.

Charles River CD Sprague-Dawley rats (60/sex/group) were fed diets containing folpet at 0, 200, 800 or 3200 ppm for 104 weeks (U.S. EPA, 1986). Ten rats/sex/group were killed at 52 weeks; few if any tumors were observed in the animals at the interim sacrifice. At termination, compound-related increases in the incidence of hyperkeratosis/acanthosis of the stomach were noted in males and females fed the mid- and high-dose. Possible compound-related increases in the incidence of adenoma/carcinoma of the thyroid and interstitial cell tumors of the testes were noted. Historical control data have been requested, but not received from the performing laboratory; the study will be reevaluated. The OPP peer review committee noted that the maximum tolerated dose (MTD) may not have been achieved, since no adverse effects on body weight or food consumption were seen.

Charles River Fischer 344 rats (60/sex/group) were fed diets containing folpet at 0, 500, 1000 or 2000 ppm (U.S. EPA, 1986). Since the high dose in this study was lower than that used in the

above study with Sprague-Dawley rats, the MTD may not have been achieved. The study has not been reviewed by EPA because it was only recently submitted. However, when the tumor incidence was compared with that in the concurrent controls, the registrant found increases ($p < 0.05$) in C-cell adenomas in the thyroid in females fed the high-dose, but not in males. There were statistically significant increases in mammary gland benign fibroepithelial tumors and in malignant lymphomas when the incidences in males and females were combined. The C-cell hyperplasia of the thyroid in males fed the low- and mid-dose were significantly increased but all animals were not evaluated for histopathology.

II.A.4. Supporting Data for Carcinogenicity

Folpet was positive in gene mutation tests: *S. typhimurium* (his), *E. coli* (WP2), mouse lymphoma (L5178Y), *E. coli* (WP2), and sex-linked recessive assays in *Drosophila*; DNA repair assays (*B. subtilis*, *E. coli* and WI-38 fibroblasts) and caused mitotic recombination (U.S. EPA, 1986). Mutagenic activity was usually reduced upon addition of hepatic homogenates. Folpet was negative in the rat bone marrow cytogenetic and mouse somatic cell mutation assays (U.S. EPA, 1986).

Folpet is structurally related to captan, which induces duodenal tumors in CD-1 and B6C3F1 mice. Folpet is rapidly degraded in vitro to phthalimide in the presence of human blood. A proposed degradation product of folpet is thiophosgene, a known metabolite of captan (U.S. EPA, 1986).

II.B. Quantitative Estimate of Carcinogenic Risk from Oral Exposure

II.B.1. Summary of Risk Estimates

Oral Slope Factor — $3.5E-3/\text{mg}/\text{kg}/\text{day}$

Drinking Water Unit Risk — $1.0E-7/\text{ug}/\text{L}$

Extrapolation Method — linearized multistage procedure, extra risk

Drinking Water Concentrations at Specified Risk Levels:

Risk Level	Concentration
E-4 (1 in 10,000)	1E+3 ug/L
E-5 (1 in 100,000)	1E+2 ug/L
E-6 (1 in 1,000,000)	1E+1 ug/L

II.B.2. Dose-Response Data (Carcinogenicity, Oral Exposure)

Tumor Type: digestive tract tumors (adenoma and/or adenocarcinoma)

Test animals: mouse/CD1, males and females

Route: diet

Reference: Chevron, 1982

Administered Dose (ppm)	Human Equivalent Dose (mg/kg/day)	Tumor Incidence
Males		
0	0	1/104
1,000	7.4	2/80
5,000	40.2	8/80
12,000	102.6	41/80
Females		
0	0	0/104
1,000	7.6	1/80
5,000	41.2	8/80
12,000	102.7	41/80

II.B.3. Additional Comments (Carcinogenicity, Oral Exposure)

Total incidences of tumors of the digestive tract (duodenum, jejunum, ileum, cecum and colon) of CD-1 mice of both sexes were combined and used to quantify human risk. The human equivalent dose was determined by assuming an average animal weight of 30 g and an average human weight of 60 kg. The slope factor of 3.5E-3 was obtained by applying the model to the combined incidence data above. The data for rats were not used pending further review of the studies.

The unit risk should not be used if the water concentration exceeds 1E+5 ug/L, since above this concentration the slope factor may differ from that stated.

II.B.4. Discussion of Confidence (Carcinogenicity, Oral Exposure)

Tumors of the duodenum are relatively rare and were seen in two strains of mice (CD-1 and B6C3F1). Relatively large numbers of animals were treated and observed for 2 years. Slope factors calculated from male and female incidence data above were 3.7E-3/mg/kg/day and 3.5E-3/mg/kg/day, respectively.

II.C. Quantitative Estimate of Carcinogenic Risk from Inhalation Exposure

Not available.

II.D. EPA Documentation, Review, and Contacts (Carcinogenicity Assessment)

II.D.1. EPA Documentation

Source Document — U.S. EPA, 1986

The Toxicology Branch Peer Review Committee, Office of Pesticide Programs, Office of Pesticides and Toxic Substances, reviewed data on folpet.

II.D.2. EPA Review (Carcinogenicity Assessment)

Agency Work Group Review — 10/07/1987

Verification Date — 10/07/1987

Screening-Level Literature Review Findings — A screening-level review conducted by an EPA contractor of the more recent toxicology literature pertinent to the cancer assessment for Folpet conducted in November 2001 identified one or more significant new studies. IRIS users may request the references for those studies from the IRIS Hotline at hotline.iris@epa.gov or (202)566-1676.

II.D.3. EPA Contacts (Carcinogenicity Assessment)

Please contact the IRIS Hotline for all questions concerning this assessment or IRIS, in general, at (202)566-1676 (phone), (202)566-1749 (FAX) or hotline.iris@epa.gov (internet address).

III. [reserved]

IV. [reserved]

V. [reserved]

VI. Bibliography

Substance Name — Folpet
CASRN — 133-07-3

VI.A. Oral RfD References

Chevron Chemical Company. 1983. MRID No. 00132457. Available from EPA. Write to FOI, EPA, Washington, DC 20460.

Chevron Chemical Company. 1984. MRID No. 00160432. Available from EPA. Write to FOI, EPA, Washington, DC 20460.

Chevron Chemical Company. 1985a. MRID No. 00151489. Available from EPA. Write to FOI, EPA, Washington, DC 20460.

Chevron Chemical Company. 1985b. MRID No. 00151560. Available from EPA. Write to FOI, EPA, Washington, DC 20460.

Chevron Chemical Company. 1985c. MRID No. 00155617. Available from EPA. Write to FOI, EPA, Washington, DC 20460.

Chevron Chemical Company. 1986. MRID No. 00161315. Available from EPA. Write to FOI, EPA, Washington, DC 20460.

VI.B. Inhalation RfC References

None

VI.C. Carcinogenicity Assessment References

Chevron Chemical Corporation. 1982. Chevron study: Lifetime oncogenicity feeding study of pholton technical (SX-946; folpet) in CD-1 (ICR derived) mice. August 24. Social Study No. 1331. (Cited in U.S. EPA, 1986)

Innes, J.R.M., B.M. Ulland, M.G. Valerio, et al. 1969. Bioassay of pesticides and industrial chemicals for tumorigenicity in mice: A preliminary note. J. Natl. Cancer Inst. 42(6): 1101-1114.

Makhteshim. 1985. Makhteshim study: Folpan oncongenicity study in the mouse. Y. Rubin and A. Nyska, September. Study No. MAK/015/FOL. (Cited in U.S. EPA, 1986)

U.S. EPA. 1986. Toxicology Branch Peer Review Committee, Office of Pesticide Programs, Office of Pesticides and Toxic Substances memorandum on folpet. July 14.

VII. Revision History

Substance Name — Folpet
CASRN — 133-07-3

Date	Section	Description
08/22/1988	II.	Carcinogen summary on-line
12/03/2002	I.A.6., II.D.2.	Screening-Level Literature Review Findings message has been added.

VIII. Synonyms

Substance Name — Folpet
CASRN — 133-07-3
Last Revised — 09/30/1987

- 133-07-3
- FOLPAN
- Folpet
- FTALAN
- 1H-ISOINDOLE-1,3(2H)-DIONE, 2-((TRICHLOROMETHYL)THIO)-
- N-(TRICHLOR-METHYLTHIO)-PHTHALAMID
- N-(TRICHLORMETHYLTHIO)PHTHALIMIDE
- N-(TRICHLOROMETHYLMERCPATO)PHTHALIMIDE
- N-(TRICHLOROMETHYLTHIO)PHTHALIMIDE
- ORTHOPHALTAN
- PHALTAN
- PHTHALTAN
- THIOPHAL
- 2-((TRICHLOROMETHYL)THIO)-1H-ISOINDOLE-1,3(2H)-DIONE
- TROYSAN ANTI-MILDEW O

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